Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	Unknown
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Glucose-6-Phosphate Dehydrogenase Deficiency (G6PD) Sequencing

ARUP test code 3004457

Spcm G6PD	Whole Blood
G6PD Interp	Positive

RESULT
One pathogenic variant was detected in the G6PD gene.

PATHOGENIC VARIANT
Gene: G6PD (NM_001042351.2)
Nucleic Acid Change: c.563C>T; Hemizygous
Amino Acid Alteration: p.Ser188Phe
Inheritance: X-linked

INTERPRETATION
One copy of a pathogenic variant, c.563C>T; p.Ser188Phe, was detected in the G6PD gene by massively parallel sequencing. Pathogenic G6PD variants are inherited in an X-linked manner and are associated with glucose-6-phosphate dehydrogenase (G6PD) deficiency (MIM: 300908). Therefore, this individual is predicted to be affected with G6PD deficiency. All female offspring will inherit the variant and be at-risk for G6PD deficiency while male offspring will not inherit the variant.

Please refer to the background information included in this report for the methodology and limitations of this test.

Evidence for variant classification:
The G6PD c.563C>T; p.Ser188Phe variant (rs5030868), also known as G6PD Mediterranean, is reported in the literature in multiple individuals affected with hemolytic anemia, hyperbilirubinemia and G6PD deficiency (Hellani 2009, Jamornthanyawat 2014, Kaplan 1997, Moiz 2012 Molou 2014 Vulliamy 1988). Functional analyses of the variant protein shows decreased enzyme activity increased affinity for G6P and decreased in vitro thermostability (Moiz 2012, Molou 2014, Vulliamy 1988). This variant is reported in ClinVar (Variation ID: 100057). This variant is found predominantly in the South Asian population with an allele frequency of 1.7% (331/19,078 alleles, including 4 homozygotes and 211 hemizygotes) in the Genome Aggregation Database. The serine at codon 188 is moderately conserved, but computational analyses predict that this variant is deleterious (REVEL: 0.811). Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Hematologic and genetic consultations are recommended. Family members should be offered testing for the identified pathogenic G6PD variant (Familial Targeted Sequencing, ARUP test code 3005867).

H=High, L=Low, *=Abnormal, C=Critical

COMMENTS
Likely benign and benign variants are not reported.
Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical limitations:
NONE

REFERENCES
Hellani A et al. G6PD Mediterranean S188F codon mutation is common among Saudi sickle cell patients and increases the risk of stroke. Genet Test Mol Biomarkers. 2009 Aug;13(4):449-52.
Jamornthanyawat N et al. A population survey of the glucose-6-phosphate dehydrogenase (G6PD) 563C>T (Mediterranean) mutation in Afghanistan. PLoS One. 2014 Feb 21;9(2):e88605.
Kaplan M et al. Gilbert syndrome and glucose-6-phosphate dehydrogenase deficiency: a dose-dependent genetic interaction crucial to neonatal hyperbilirubinemia. Proc Natl Acad Sci U S A. 1997 Oct 28;94(22):12128-32.
Moiz B et al. Neonatal hyperbilirubinemia in infants with G6PD c.563C > T Variant. BMC Pediatr. 2012 Aug 20;12:126.
Molou E et al. Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency in Greek newborns: the Mediterranean C563T mutation screening. Scand J Clin Lab Invest. 2014 Apr;74(3):259-63.
Vulliamy TJ et al. Diverse point mutations in the human glucose-6-phosphate dehydrogenase gene cause enzyme deficiency and mild or severe hemolytic anemia. Proc Natl Acad Sci U S A. 1988 Jul;85(14):5171-5.

This result has been reviewed and approved [redacted]

BACKGROUND INFORMATION: Glucose-6-Phosphate Dehydrogenase Deficiency (G6PD) Sequencing

CHARACTERISTICS: Although G6PD deficiency is usually asymptomatic, it can result in episodic hemolytic anemia triggered by infections, specific foods, and drugs. In newborns, it may be causal for life-threatening acute hemolytic anemia with jaundice. Variants are classified as follows: Class I - severe enzyme deficiency associated with chronic nonspherocytic hemolytic anemia; Class II - severe enzyme deficiency (<10 percent of normal activity); Class III - mild to moderate enzyme deficiency (10-60 percent of normal activity); and Class IV - normal range (>60 percent of normal enzyme activity). G6PD deficiency is best managed by avoiding known environmental triggers. For a list of drugs that may cause adverse reactions in individuals with G6PD deficiency refer to: https://cpicpgx.org/genes-drugs/.
EPIDEMIOLOGY: Highly variable but ranges between 5-30 percent in males of African, Asian, Mediterranean, and Middle Eastern descent.

CAUSE: Hemizygosity for a pathogenic G6PD germline variant in men, and homozygosity or compound heterozygosity in women. Some heterozygous women may be affected due to skewed X-chromosome inactivation.

INHERITANCE: X-linked.

PENETRANCE: Low.

CLINICAL SENSITIVITY: 98 percent.

GENE TESTED: G6PD (NM_001042351)

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the G6PD gene, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and to confirm reported variants that do not meet acceptable quality metrics. Human genome build 19 (Hg 19) was used for data analysis.

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ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions (indels) from 1-10 base pairs in size. Indels greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced. Specificity is greater than 99.9 percent for all variant classes.

LIMITATIONS: A negative result does not exclude a diagnosis of G6PD deficiency. This test only detects variants within the coding regions and intron-exon boundaries of the G6PD gene. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants, deep intronic variants, and large deletions/duplications will not be identified. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations caused by the presence of pseudogenes, repetitive, or homologous regions. This test is not intended to detect low-level mosaic or somatic variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA) variants, or repeat expansions. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the U.S. Food and Drug Administration. This test was performed in a CLIA-certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Spcm G6PD	22-301-104647	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
G6PD Interp	22-301-104647	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

H=High, L=Low, *=Abnormal, C=Critical